CNS Drugs (2018) 32:939–949
https://doi.org/10.1007/s40263-018-0564-y

REVIEW ARTICLE

Cancer Risk in Patients with Multiple Sclerosis: Potential Impact of Disease-Modifying Drugs

Christine Lebrun[1] · **Fanny Rocher**[2]

Published online: 24 August 2018

Abstract

In the 1990s, the first disease-modifying therapies (DMTs) for multiple sclerosis (MS) were injectable immunomodulatory (IM) drugs, including four different interferon-β preparations and glatiramer acetate. Since 2000, more than 15 immunosuppressant (IS) drugs have been used, with a more or less specific action on inflammation. These include monoclonal antibodies targeting CTL4, the integrin receptor, the interleukin (IL)-2 receptor, CD19, CD20, CD52, and the sphingosine 1 phosphate family. The association between MS and cancer has long been investigated but has led to conflicting results. No studies have reported an increased risk of cancer after long-term exposure to IM. Several reports suggest an increase in cancer risk among MS patients treated with IS such as mitoxantrone, azathioprine and cyclophosphamide. Because of their action on the immune system, and due to a lack of available long-term data, a special warning of the potential risk of cancer accompanies the use of recent IS such as cladribine, fingolimod, natalizumab or alemtuzumab. In most studies, factors such as diet, smoking, solar radiation, and hormone therapy, all of which influence cancer risk, have not been considered. For fingolimod, natalizumab, alemtuzumab, dimethyl fumarate, teriflunomide, daclizumab and ocrelizumab, risk management plans outlined by regulatory agencies are mandatory. They allow prospective detection of some red flags, in particular those for the increased risk of cancer. We review the current evidence behind the increased risk of malignancy in MS patients receiving DMTs, and provide an overview of the DMTs that are currently in use and those in clinical trials. The known risks and benefits of these therapies will be considered.

Key Points

Long-term management of MS with DMTs has been associated with a number of safety concerns, such as an increased risk of developing cancer.

Neurologists need to discuss with the patient the necessary surveillance measures, including careful screening and frequent monitoring, which are required to manage the increased risk of cancer. This should take into account long-term safety/toxicity and the consequences of continued exposure to multiple drugs.

The risk of cancer for individuals with MS exposed to immunosuppressants (IS) seems to be related to the duration of exposure and cumulative dose, not to a specific IS.

✉ Christine Lebrun
Lebrun.c@chu-nice.fr

[1] Centre de Ressources et Compétences Sclérose En Plaques, Neurologie, Université Nice Côte d'Azur, CHU Pasteur 2, 30 voie Romaine, 06002 Nice, France

[2] Centre Régional de Pharmacovigilance, CHU Cimiez, Nice, France

1 Introduction

Multiple sclerosis (MS) represents one of the major causes of neurological disability, especially in young adults. This disorder is known to be more common among Caucasian populations, particularly those of Northern European ancestry, and is three times more common in women than in men. The peak age at onset, for most of the cases, is between 20 and 50 years. Diagnosis is based on clinical history and physical examination, and requires dissemination of signs and symptoms in space and time [1]. In addition, magnetic resonance imaging (MRI) should show evidence of white matter plaques in the periventricular, juxtacortical/cortical or infratentorial regions of the brain or in the spinal cord [2].

The natural history of the risk of cancer has been studied and seems to not be increased, but most studies do not consider genetic susceptibility or environmental exposure [3, 4]. As for other autoimmune diseases, this chronic condition and risk of disability due to relapse has enhanced therapeutic research into prevention of the development of inflammatory attacks of the central nervous system. The impact of prolonged exposure to various disease-modifying therapies (DMTs) has been studied. In the 1980s, treatments were mostly based on

corticosteroid pulses and either off-labeled oral azathioprine, methotrexate, or cyclophosphamide. Ten years later, neurologists saw an incredible development of the therapeutic arsenal, with the possibility of using an escalating strategy. First-line treatments include immunomodulatory (IM) drugs such as subcutaneous (SC) or intramuscular interferon (IFN)-β, or SC glatiramer acetate, while for patients with a more aggressive disease course or who do not respond to first-line treatments, immunosuppressants (IS) such as intravenous mitoxantrone have been used. There has been a lot of discussion about using an induction strategy with IS versus an escalation strategy [5]. The years 2000s are marked by the introduction of new families of IS with a more specific mechanism of action, including monoclonal antibodies such as natalizumab, or sphingosine 1 phosphate (S1P) inhibitors such as fingolimod. Since 2010, new drugs have been made available each year, favoring either more specific mechanisms of action, including an anti-interleukin (IL)-2 receptor (daclizumab), anti-CD52 (alemtuzumab), anti-CD20 (rituximab, ocrelizumab), more selective anti-S1P receptors (ozanimod, ponesimod, siponimod), or oral administration such as teriflunomide, dimethyl fumarate, or cladribine. Since more than 23 drugs are available, it is possible to switch from one to another in the case of inefficacy or non-compliance; the question of whether or not these drugs increase the risk of cancer, and which ones, has been raised. Another important issue for consideration is what to do for MS patients with a history of cancer who need DMT, or patients who develop cancer when under a DMT.

An overall review of the available data on cancer in MS patients, as well as a review of each DMT is provided.

2 Methodology

An extensive search of PubMed (1 January 1980 to 31 March 2018) was performed using the following keywords: multiple sclerosis, cancer, tumor, lymphoma, interferon β, glatiramer acetate, azathioprine, mitoxantrone, daclizumab, fingolimod, natalizumab, cyclophosphamide, rituximab, ocrelizumab, teriflunomide, dimethyl fumarate, immunomodulators, and immunosuppressants. Complementary information was also implemented upon request on Vigibase®, the World Health Organization's (WHO) pharmacovigilance database, through Vigilyze®. Vigibase® is continuously updated with incoming individual case safety reports (ICSRs) from worldwide national medicine agencies. Queries were performed using each pre-cited DMT and the system organ class (SOC; from the Medical Dictionary for Regulatory Activities [MedDRA]) 'Neoplasm benign, malignant and unspecified' from drug launch to 31 March 2018.

3 Cancer Risk in Multiple Sclerosis (MS)

A systematic review of the incidence and prevalence of cancer in MS performed up to 31 March 2018 gathered together 38 studies and concluded that cervical, breast, and digestive cancers had the highest incidence. The risk of meningiomas and urinary system cancers appeared higher than expected, while the risk of pancreatic, ovarian, prostate, and testicular cancer were lower than expected [6]. The impact of age, ethnicity, and sex are usually poorly considered.

An analysis of population-based data reported a significantly decreased risk of cancer in MS patients compared with the general population [7–9]. However, conflicting data exist showing no difference in risk [3, 10] or an increased risk of cancer in MS patients [4], which may be due to differences in the study design or methods of case ascertainment [11]. Kingwell et al. raised the important concern regarding patients with MS who may experience a delay in diagnosis, which leads to a more advanced cancer at diagnosis, even if they normally benefit from closer neurological follow-up [12].

Antitumor immunosurveillance may provide a physiological explanation for the reduced cancer risk in MS patients [13, 14]. Indeed, autoimmunity is a form of hypervigilance against self-antigens, and may be one of the mechanisms leading to the development of MS. Further studies are required to address this issue, including investigation into the properties of the lymphocytes of MS patients. For most cohorts, there is no relevant difference in cancer risk between men and women [15–18]. A family history of MS or other autoimmune diseases has been associated with a higher risk of MS, suggesting a common genetic background or shared environmental triggers, influencing the occurrence of MS and cancer [19]. In most studies, there is no consideration of familial susceptibility to develop cancer or of exposures to toxic agents such as alcohol or tobacco, or the effect of physical activity or diet. MS and cancer have been reported in a BRCA1 (BReast Cancer 1)-positive family, further suggesting in some cases the role of genetics and hereditary factors [20].

4 Disease-Modifying Therapies (DMTs) in MS

4.1 Cohort Studies and Registries during the DMT Era

National MS databases or registries usually contain a very low number of patients with cancer. This points out the fact that information gathered from spontaneous reports may

underestimate the number of actual events. It also underlines the fact that physicians do not systematically report the occurrence of cancer associated with treatment for MS. For the oldest DMT, the number of reports of cancer was probably underestimated. In contrast, a dedicated database for new MS DMT, which has been made available since 2005, mentions in the extension phase of pivotal studies the existence of some cases of cancer, without a relationship to causality, but this has to be confirmed with a longer period of follow-up.

The French CARIMS (CAncer Risk In Multiple Sclerosis) study reported a threefold increased risk of cancer (p1⁄40.0035) among 7418 patients with a history of immunosuppressive therapy, with a mean follow-up of 11.5 years. The univariate analysis found a significant effect with azathioprine (p1⁄4 0.001), but not with cyclophosphamide or mitoxantrone [19]. Matched for age, the risk of cancer in MS was associated with the duration and type of IS treatment. Dose- and duration-dependent azathioprine-related toxicity has already been reported in MS patients [21].

In a recent Italian study, the cancer risk was higher in MS patients associated only with previous IS exposure compared with rates observed among an equal number of patients not exposed to IS, and to the risk in the general population in Sicily for similar age groups (adjusted hazard ratio 11.05, 95% confidence interval [CI] 1.67–73.3; $p = 0.013$) [17]. The risk of cancer observed in individuals with MS exposed to IS seems to be related to the duration of exposure and the cumulative dose, not to a specific IS. There is also a declaration bias to consider since MS patients reporting cancer were also more likely to have used a DMT.

A French case-control study reported that among MS patients, 7.32% presented with a cancer, compared with 12.63% of controls, confirming that the use of DMT, whatever the disease course, does not appear to increase the risk, even when tobacco and alcohol consumption were considered ($p = 0.42$) [9].

4.2 Immunomodulators

In the mid-1990s, IFN-β and glatiramer acetate were the first IM drugs approved for MS.

4.2.1 Interferon-β

Preclinical data provided for marketing authorization reported no cancer risk was identified. Data extracted from postmarketing surveillance in the WHO international database Vigibase®, using the Vigilyze® application, found 9774 ICSRs from first launch in 1994 to 31 March 2018. Of these cases, 1276 were breast cancers, 553 were uterine cancers, and 491 were unspecified cancers. A report assessed whether IFN-β treatment for MS was associated with a cancer risk or the risk of specific cancers in a British Columbian population-based observational study with an average of 9.5 years of follow-up [23]. The cohort included 5146 relapsing-onset MS patients and 48,705 person-years of follow-up, during which 227 cancers were diagnosed. Exposure to IFN-β was not significantly different for cases and controls (odds ratio [OR] 1.28, 95% CI 0.87–1.88). There was a non-significant trend towards an increased risk with IFN-β exposure for the breast cancer cases (OR 1.77, 95% CI 0.92–3.42), but no evidence of a dose–response effect. The size of tumors was similar for the IFN-β treated and non-treated cases. This is in agreement with the French study, which included MS patients, with or without cancer, who were followed in 12 MS centers and were included in the European Database for MS; the findings revealed no increased risk of cancer with exposure to any of the IFN-β preparations [24].

These findings contrast somewhat with those from a smaller study from Israel, which included 1338 MS patients (15 of whom developed cancer when receiving DMT), and showed a borderline association between a non-breast cancer risk and IFN-β treatment without reaching statistical significance [23]. Two industry-sponsored studies have reported no malignancy risk with IFN-β-1a (intramuscular) or IFN-β-1a (SC) treatment [26, 27]. These data were supplemented with information from clinical trials or an insurance claim database. In both situations, the observation period was likely too short to rule out a cancer risk (2–3 years).

4.2.2 Glatiramer Acetate

Glatiramer acetate (Copaxone®; Teva Pharmaceutical Industries Ltd, Kansas City, MO, USA), an injectable polypeptide IM agent, is currently approved for the treatment of relapse-remitting MS (RRMS). Although the exact mechanism of action remains unknown, glatiramer acetate appears to alter the immune function by acting on $CD8^+$ T cells, antigen-presenting cells, monocytes, and B cells, and by altering T-cell differentiation. The Summary of Product Characteristics (SmPC) of the European Medicines Agency (EMA) provided information on the risk for cutaneous cancers. A total of 1122 cases were reported in Vigibase® from 1999 to 31 March 2018, with 205 breast cancers, 54 lymphomas, and 53 malignant melanomas, but with only 20 skin cancers. A recent case report described a case of a 43-year-old woman who presented with recurrence of stage IIIb melanoma while receiving glatiramer acetate. Spontaneous resolution was observed after drug withdrawal [28].

In the Israeli study, female MS patients treated with glatiramer acetate showed an elevated number of breast cancers [25]. These results were not confirmed later, but another study demonstrated a higher degree of co-expression of lymphocyte (regulatory T cell) populations in tumors with

a high histological grade, negative estrogen receptor status, and increased lymphocytic infiltration [29]. These data suggest that further study is warranted to help elucidate the possible connections between breast cancer prognoses in patients with MS treated with glatiramer acetate.

In the British Columbian cohort, 2.6% of the 233 cases had a history of exposure to glatiramer acetate, and their treatment history did not differ from the controls (OR 1.06, 95% CI 0.46–2.49), especially for breast cancer [23]. This has also been described in the French CARIMS study, in which no increased risk was described, even with long-term exposure [24]. Several T-cell-mediated skin conditions have been associated with the use of glatiramer acetate, such as pseudolymphoma, including drug eruptions, and erythema nodosum. A CD30+, primary, cutaneous, anaplastic, large-cell lymphoma that developed after initiation of glatiramer acetate therapy has been reported [30].

In accordance with current knowledge regarding classical IM, there is no increased risk of cancer in patients who received first-line DMT [23, 24]. These findings are reassuring for the real-world clinical setting; the overall cancer risk does not appear to be increased by exposure to IFN-β or glatiramer acetate in either men or women with MS. Nevertheless, healthcare professionals should pay attention to performing careful follow-up, reassuring MS patients but encouraging regularly check-ups with specific specialists, such as gynecologists or dermatologists.

4.3 Immunosuppressants (IS)

Fewer studies have focused on the impact of IS on cancer risk in MS patients. Some studies suggest an increased cancer risk for patients who received azathioprine, cyclophosphamide, or several IS lines of treatment [21, 24]. Another study recently showed that the overall incidence of malignancies was only slightly increased in patients who received mitoxantrone, except for the risk of leukemia and colorectal cancer, which was higher [29]. Notwithstanding, the cancer risk of such treatments is well known for indications other than MS [31, 32]. Rheumatoid arthritis or Gougerot Sjögren patients receiving methotrexate have an increased risk of lymphoma, but it seems that this risk is linked to the disease and not its treatment [33]. This once again suggests that what has been described in some autoimmune diseases cannot be extended directly to MS. The possibility that MS patients may hold a protective status against cancer, as has been hypothesized for immune-mediated diseases, but a higher intrinsic susceptibility to cancer if exposed to DMT, has not been confirmed [6].

The risk of developing cancer, observed in individuals with MS exposed to IS, seems to be related to the duration of exposure and the cumulative dose, but not to a specific IS. This could be related to the fact that some of these drugs are classified as IS but have an IM effect. It is noteworthy that several DMTs are also used, or are being evaluated for their potential antitumor activity. Examples include dimethyl fumarate, which induces necroptosis in colon cancer cells [34]; fingolimod, which is being tested for the treatment of various cancers to increase the efficacy of other drugs [35]; and teriflunomide, which has been shown to have anticancer activity against triple-negative breast cancer cells [36]. Mitoxantrone is a well-known antineoplastic drug. Cladribine can be associated with alemtuzumab, based on its epigenetic properties for the treatment of lymphoid leukemia, reversing the histone deacetylase (HDAC) resistance of this disease [37, 38]. Thus, DMTs may inhibit cancer development in some cases, although they are administered differently in oncological indications.

4.3.1 Mitoxantrone (Elsep®)

Mitoxantrone is the only global cytotoxic IS validated for MS, but its cardiac and hematological toxicity limit its use to aggressive forms. The cumulative dose is limited to 140 mg/m^2 because of this cardiotoxicity. When treated with mitoxantrone, MS patients must be monitored for cardiac and hematologic abnormalities for at least 5 years [39]. In 2005, subsequent to reports of leukemia, the US FDA instituted a ‘black box’ warning and National Health Authorities were alerted to this risk. The SmPC also contains alerts and recommendations on careful patient monitoring every 3 months during treatment and for up to at least 5 years after mitoxantrone discontinuation.

Extraction of cases from Vigilyze® to 31 March 2018 identified 940 cases of cancer in mitoxantrone-treated patients, including 221 cases of acute leukemia and 89 cases of myelodysplastic syndrome. The previous Italian cohort concluded that the risk of treatment-related acute myeloid leukemia (TRAL) was higher than expected (27%) [39]. Although estimates of the incidence of TRAL after therapy with mitoxantrone vary considerably, a meta-analysis of data from 15 recent large case series showed a 3-year mitoxantrone-related leukemia incidence of 0.33% in 5472 mitoxantrone-treated patients with MS [40]. The meta-analysis reported an increase in TRAL when patients were exposed to more than 60 mg/m^2, with a mortality rate from leukemia of 24% [40]. A report from the American Academy of Neurology specifies a risk of 0.8% for TRAL [41]. Other case series reported lower rates of TRAL: in a class III retrospective study of 100 consecutive French patients who received induction with monthly mitoxantrone boluses for 6 months (max 72 mg/m^2), one patient (previously reported

in a larger cohort) developed acute myelogenous leukemia [42].

A retrospective observational cohort of 676 patients with a median follow-up of 8.7 years identified 37 patients (5.5%) with a malignancy after mitoxantrone initiation, revealing a standardized incidence ratio (SIR) of 1.50. The SIRs of colorectal cancer and acute myeloid leukemia were 2.98 and 10.44, respectively, with no increase for other entities, including breast cancer [31]. An interesting study demonstrated that single nucleotide polymorphisms in double-strand break repair genes might confer predisposition to leukemia. The association of homozygous variants of BRCA2 and XRCC5 yielded a higher risk of TRAL as it may be linked to genetic variants in DNA repair and drug-metabolizing enzymes that result in impaired detoxification of chemotherapy or inefficient repair of drug-induced genetic damage [43].

4.3.2 Fumaric Acid (Tecfidera®)

The mechanism by which dimethyl fumarate exerts therapeutic effects in MS is not fully understood, but studies demonstrated anti-inflammatory and IM properties by reducing immune cell activation and subsequent release of proinflammatory cytokines in response to inflammatory stimuli. Preclinical studies into carcinogenesis reported an increased incidence of renal tubular carcinoma and squamous cell papilloma, and carcinomas in the non-glandular stomach (forestomach) of rodents. A recent French postmarketing survey from November 2017 cumulated 32 reports of neoplasm, mainly of breast (8) and skin (2 melanoma, 2 basocellular, 2 unspecified).

Data from the German Psoriasis Registry PsoBest identified an overall rate of serious adverse events of 1.3/100 patient-years with conventional systemic drugs, and 1.5/100 patient-years with biological drugs; a lack of significant between-treatment differences was found for the rate (per 100 patient-years for conventional systemic drugs vs. biological drugs) of malignancies, excluding non-melanoma skin cancer (0.46 vs. 0.49) [44]. Few data are available regarding potential malignancies for MS patients receiving dimethyl fumarate; malignancies are an important potential risk of the risk management plan and remain a safety concern for close monitoring.

4.3.3 Teriflunomide (Aubagio®)

This is a selective IS agent that reduces the lymphocyte count by inhibiting pyrimidine synthesis. Due to its IS effect, there is a theoretical risk of malignancy. This potential risk has been underlined in the SmPC (class effect). However, to date no sign of cancer has been identified in the preclinical and clinical data; teriflunomide was not found to be mutagenic in vitro or clastogenic in vivo, and no evidence of carcinogenicity was observed in rats and mice. The French postmarketing survey analysis performed in December 2015 did not detect any red flags of cancer. To 31 March 2018, Vigilyze® identified 308 cases of cancer, again mostly breast (47) and skin (11) cancers. An isolated case of follicular lymphoma was reported in a 54 year-old MS patient after 8 months of treatment [45].

4.3.4 Fingolimod (Gilenya®)

Various case reports have related the occurrence of cancers in fingolimod-treated patients involving the lungs, brain, and hematopoietic and lymphatic systems, but mostly various types of skin cancers. Overall, 1864 cases of malignancies were reported in Vigibase® from 2006 to 31 March 2018, mainly consisting of cases of basocellular carcinoma (272), breast cancer (168), and multiple myeloma (132). Sphingolipids and sphingomyelin derivates, such as sphingosine, have attracted attention for their effect on epidermal cells. It has been demonstrated that some components may either inhibit or promote metastasis in a mouse melanoma model [46]. Malignant neoplasms were reported in four patients receiving 0.5 mg of fingolimod, four patients receiving 1.25 mg of fingolimod (one breast cancer, one Bowen's disease, and two skin cancers), and 10 patients receiving placebo. In the FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in MS) study, a 24-month, double-blind, randomized study comparing fingolimod with IFN-ß-1a in 1033 patients (702 were enrolled in the fingolimod group), 12 cancers (five basal cell carcinomas, four breast cancers, three melanomas) were reported, compared with one basal cell carcinoma in the IFN-β-1a group [47]. The use of drugs, such as fingolimod, which inhibit sphingosine, raises the question of dermatological monitoring.

Two recent publications reported Merkel cell carcinoma (MCC), a rare and aggressive neuroendocrine skin cancer [48]. For these tumors, diagnosis was confirmed by a strong diffuse positivity of the MCPyV T-antigen (Merkel cell polyomavirus) on immunohistochemistry of a skin biopsy of the tumor. A causal connection between fingolimod and MCPyV-related MCC has been suggested to occur with the drug in association with both neoplasms and reactivation of viruses.

A Dutch study reported five cases of superficial spreading of malignant melanoma, with a higher incidence than expected [49]. The recently published TRANSFORM (Trial Assessing Injectable Interferon Versus FTY720 Oral in RRMS) long-term follow-up study confirms these observations, showing an increased incidence of non-melanoma skin cancer (NMSC) and no increased incidence of melanoma

in patients followed for up to 4.5 years [50]. A case of cutaneous CD30+ T-cell lymphoma (CTCL) was recently described [51]. A few cases of lymphomatoid papulosis and B- and T-cell lymphoma, as well as a single case of acute lymphoblastic leukemia, have recently been published [52, 53]. The causality of fingolimod in this case was suspected by the fact that the skin lesions appeared after the commencement of treatment and resolved rapidly after discontinuation of therapy. A case of Kaposi sarcoma, a low-grade skin tumor related to HHV-8, in a fingolimod-treated patient has been published [54]. Lastly, in 2015, when considering the risk of basal cell carcinoma, the EMA recommended medical evaluation of the skin before starting treatment, after at least 1 year, and then at least yearly during treatment with fingolimod. Gilenya® must not be used in patients with either basal cell carcinoma or any other type of cancer. The SmPC provides clear information on the increased risk of lymphoma and cutaneous cancer, and recommended an annual dermatological check-up.

In France, The VIRGILE study, a 2-year pharmacoepidemiological study, including a medicoeconomic analysis, requested by French Health Authorities (HAS and CEPS), reported on 8 cancers in 1023 patients treated with fingolimod, with one patient who died of lung cancer after 52 days of fingolimod, in contrast to two cancers among 321 patients treated with natalizumab [55]. To date, the difference is considered as non-significant, but it is mandatory to wait for definitive results.

4.3.5 Cladribine (Mavenclad®)

Cladribine is a synthetic purine analog that is cytotoxic to lymphocytes and, to a lesser degree, monocytes and hematopoietic cells. A large phase III study (CLARITY), which was subsequently extended, demonstrated its efficacy in RRMS [56]. Oral cladribine administered over 10 days (total dose 3.5 mg/kg) at years 1 and 2 induced prolonged non-selective lymphopenia, which underlies its therapeutic effect. Cladribine was first authorized in Australia but the license was initially rejected by the EMA in 2013 due to a suspected increase in cancer risk. Numerous studies reported cancers after cladribine treatment in various indications other than MS [56, 57]. The pharmaceutical company decided to withdraw the drug from the market and to perform additional studies before submitting it again for approval. Three cases of cancer occurred in patients treated with 3.5 mg/kg of cladribine (one melanoma, one pancreatic cancer, and one ovarian cancer) [58]. One choriocarcinoma was reported in the 5 mg/kg arm 9 months after the end of the study.

A meta-analysis of 11 phase III trials demonstrated that there was no evidence of a higher risk of cancer in patients with MS taking cladribine compared with IM or IS, including dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, or teriflunomide [59]. These data are supported by the long-term outcome of people with leukemia treated with cladribine in whom no increase in second malignancies was detected [60]. Despite its pharmacological genotoxicity potential, long-term studies on rodents and monkeys did not reveal increased carcinogenicity that could be extrapolated to humans.

As of 2017, Mavenclad® has been approved by the FDA and EMA for the treatment of active MS. The SmPC provides Information regarding increased cases of malignancies in treated patients compared with placebo-exposed patients. Caution should be paid when using Mavencald®, and long-term follow-up of exposed patients may be proposed.

4.3.6 Alemtuzumab (Lemtrada®)

Alemtuzumab is a humanized monoclonal antibody that depletes circulating lymphocytes by selectively targeting CD52, which is expressed at high levels on T and B lymphocytes. It is approved for the treatment of adults with active RRMS. No cancer cases have been reported in the French safety database to 31 March 2017 (there was one report of uterine fibroma, and one report of human papillomavirus anogenital warts for neoplastic events). Analysis of Vigilyze® retrieved 527 cases to 31 March 2018, mostly lymphoproliferative syndrome (45) and underlying cancer progression (30). In the CARE-MS (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis) II 5-year follow-up, two malignancies (papillary thyroid microcarcinoma and melanoma) were reported in years 3–5. Over 5 years, a total of four malignancies were reported (one case of thyroid cancer and one case of basal cell carcinoma occurring in the core study) [61]. In CARE-MS I, over 5 years, a total of six malignancies were reported in alemtuzumab-treated patients (exposure-adjusted incidence rate of 0.3/100 patient-years). Two malignancies occurred in the core study (both papillary thyroid carcinomas), and four malignancies were reported in years 3–5 ($n = 5$; one each for breast cancer, keratoacanthoma, non-small cell lung cancer, and micropapillary thyroid carcinoma) [62]. Another case of melanoma was described but no direct imputability was drawn [63]. Caution regarding the theoretical risk of developing malignancies is mentioned in the SmPC.

4.3.7 Natalizumab (Tysabri®)

Natalizumab, an α4 integrin antagonist that blocks attachment to cerebral endothelial cells and thus reduces inflammation at the blood-brain barrier, was approved by the FDA

in 2004. In the AFFIRM (nAtalizumab saFety and eFficacy In Relapsing-remitting Multiple Sclerosis) study, six cases of cancer were reported in association with natalizumab treatment—one case (<1%) in the placebo group and five cases (<1%) in the natalizumab group, but some patients had received DMT before natalizumab [64]. The five cases of cancer that occurred in natalizumab-treated patients included three cases of breast cancer, one case of stage 0 cervical cancer, and one case of newly diagnosed metastatic melanoma. There was one case of basal cell carcinoma in the placebo group.

The last report of a postmarketing survey does not show an increase in expected cases of cancer with (to 1 December 2011) 36 reports of cancers: breast (8), skin (4 melanoma, 2 basal cellular carcinomas), hematological (2 chronic leukemia, 2 lymphoma, 1 acute leukemia after mitoxantrone treatment), and colorectal (3). Special attention has been given to the occurrence of melanoma. Neurologists have questioned whether there is a cause-and-effect relationship between the use of natalizumab and melanoma in MS patients [65]. Antibodies against α4 integrins could favor the locoregional spread of melanoma by downregulating the immune system. To date, by combining clinical trials and postmarketing data, the incidence of melanoma is estimated at approximately 5/100,000 MS person-years treated with natalizumab. Longitudinal follow-up with videodermoscopy of natalizumab-treated patients showed some modification in pigmented lesions, but no aggressiveness of known nevi [66].

To 31 March 2018, there were 3385 reports of malignancies in VigiBase®, including 375 breast cancers and 150 melanomas. In May 2015, 16 cases of central nervous system diffuse large B-cell lymphomas (CNSL) were identified in association with natalizumab in VigiBase®, the WHO international database of suspected adverse drug reactions, from five countries [67]. Five isolated case reports of CNSL have been published, four of which were already present in VigiBase®. Analysis of these cases suggests that natalizumab may play a role in rapid progression of the CNSL. For other neoplasms, no distinct differences in the incidence rates has yet emerged from the provided data set, but malignancies are an important potential risk, which is closely followed in the risk management plan for natalizumab.

4.3.8 Daclizumab (Zymbrita®)

Daclizumab is a humanized SC immunoglobulin (Ig) G1 monoclonal antibody that has demonstrated efficacy in RRMS [68, 69]. It has a high-yield process, conferring a different glycosylation profile that leads to a reduction in cellular cytotoxicity. While the EMA approved daclizumab for the treatment of adults with relapsing forms of MS, due to safety concerns the FDA recommended use of daclizumab in patients who had an inadequate response to at least two first-line DMTs. Preclinical safety studies of carcinogenesis and mutagenesis have not been conducted. However, no pre-neoplastic or neoplastic tissue has been observed in two 9-month studies performed with monkeys. In the first 3-year, open-label SELECTED extension study, published in 2016, clinical efficacy was sustained with a similar safety profile [70]. Nineteen of 2236 patients (0.8%; $N = 19$) had a malignancy. No patterns in the types and rates of malignancies reported were observed. Since few safety data are available to date for MS patients, additional postmarketing pharmacovigilance reports are necessary to assess further potential serious adverse events that can be associated with the use of daclizumab. In March 2018, the EMA recommended the immediate suspension and recall of the drug subsequent to 12 reports worldwide of serious inflammatory brain disorders, which may also be linked to severe immune reactions affecting several other organs.

4.3.9 Ocrelizumab (Ocrevus®), Rituximab (Mabthera®)

Rituximab (Roche, Genentech), an anti-CD20 monoclonal antibody, has been prescribed off-label worldwide for many years for all types of MS; however, in March 2017 and January 2018, respectively, ocrelizumab, a humanized anti-CD20 monoclonal antibody, was approved by the FDA and the EMA for the treatment of relapsing forms of MS (OPERA I and II) and primary-progressive (ORATORIO) MS [71, 72]. To date, the OPERA trial has reported six malignancies: mantle cell lymphoma and squamous cell carcinoma in the IFN-β-1a arm, and renal cancer, melanoma, and two breast cancers in the ocrelizumab arm. In the ORATORIO trial, 11 malignancies were reported in the ocrelizumab arm, compared with two in the placebo-treated patients. A Vigilyze® search on 31 March 2018 gave 3853 malignancies for rituximab-treated patients. Most cases related to hematological cancers, such as myelodysplastic syndrome (362), acute leukemia (202), and lymphoma (197), but very few data related to MS patients. If considered as a class effect, the rate of serious infections and the incidence of malignancies were not increased in rheumatoid arthritis patients treated with rituximab over a 9.5-year follow-up, which is quite reassuring [73].

The development of further phase III trials with other anti-CD20 monoclonal antibodies are ongoing: ofatumumab (Genmab/Novartis), a fully human anti-CD20 monoclonal antibody, is currently being evaluated in randomized, phase III, double-blind trials (ASCLEPIOS I and II), as is ublituximab (TG Therapeutics), a chimeric anti-CD20 monoclonal antibody that has been glyco-engineered to enhance the affinity for all variants of FcyRIIIa receptors and to increase the antibody-dependent cell-mediated cytotoxicity.

4.4 Off-Label IS

4.4.1 Azathioprine (Imurel®)

Azathioprine is a purine antagonist that affects DNA replication and the immune system in various ways. It impairs T-cell lymphocyte function and is more selective for T lymphocytes than B lymphocytes. Neurologists have used it off-label for more than 30 years, before more specific DMTs become available. A review of seven clinical studies evaluating the effect of azathioprine in MS, up to 1989, concluded that it was efficacious in relapsing forms [74]. A total of 380 cancer cases were reported in VigiBase® from 1972 to 31 March 2018; 178 of these cases were basal cell carcinomas, 155 were squamous cell carcinomas, and 125 were lymphomas in a population not restricted to MS patients.

Many publications on the potential malignant risk with azathioprine for label-exposed patients can be retrieved. However, conflicting conclusions on the potential risk of malignancy in MS patients with long-term azathioprine treatment have been put forward [75]. A possible increase in risk was only reported for treatment duration beyond 10 years or over a 600 g cumulative dose [22]. A dose effect was also reported for myelodysplastic syndrome and cutaneous malignancies after long-term treatment with azathioprine in MS.

Warnings on the risk of cancer with IS drugs such as azathioprine appear in the SmPC, particularly with regard to the risk of lymphoproliferative syndrome, cutaneous cancer, and uterine cancer. The identified risk factors include total time of treatment and intensity of immunosuppression. There is also mention of possible regression of non-Hodgkins lymphoma and Kaposi sarcoma. In fact neurologists should make patients aware of the possible increased risk of malignancy related to long-term (>10 years) treatment.

4.4.2 Cyclophosphamide (Endoxan®)

Intravenous cyclophosphamide is used in progressive forms of MS, in view of its reported efficacy and safety in the short-term. This cytotoxic drug may expose patients to other autoimmune diseases or lymphoma, and to a dose-dependent long-term risk of bladder cancer [76]. Given its pharmacological mechanism of action, its carcinogenic potential is still to be reported, and the SmPC provides information on the risk of developing solid tumors as well as hematological disorders. In fact, 5273 cases of malignancies were reported in VigiBase® from 1971 to 31 March 2018; 642 were cases of myelodysplastic syndrome and 635 were cases of acute myeloid leukemia, but for patients treated for diseases other than MS and who received multiple treatment lines, including antineoplastic drugs such as doxorubicin.

Cases of bladder cancer have been identified in a retrospective study of 2351 patients with MS. Seven (0.29%) patients had bladder cancer, six of whom had an indwelling catheter for >1 year, and one who had undergone intermittent catheterization. Of the 70 patients who received cyclophosphamide, five (5.7%) had bladder cancer; these patients all had an indwelling catheter [77]. High cumulative cyclophosphamide doses are associated with an increased risk of acute myeloid leukemia and non-melanoma skin cancers, but this has not been demonstrated in MS. A French historical prospective study on a cohort of cyclophosphamide-treated MS patients studied the cancer incidence and compared it with the incidence in the general population by estimating SIRs [78]. Among 354 patients with a median follow-up of 5 years (2-15), 15 developed solid tumors. The cumulative incidence of cancer after cyclophosphamide was 3.1% at 5 years, and 5.9% at 8 years. No increase in cancer incidence after cyclophosphamide treatment was found. This negative result, apparently contradictory to the well-documented, dose-dependent toxicity of cyclophosphamide in other autoimmune diseases, may be explained by the fact that patients were limited to low cumulative doses, by systematic use of the uroprotective agent mesna, the patient's behavior in lowering exposure to tobacco or alcohol abuse, or the decrease in genetic susceptibility of MS patients to developing cancer.

5 Clinical Management of DMTs for MS Patients in Neurological Practice

In the 2018, ECTRIMS/EAN (European Committee for Treatments and Research In Multiple Sclerosis/European Association of Neurology) guidelines on the pharmacological treatment of patients with MS, there is a topic that insists on the complexity of the treatment decision and follow-up of MS patients by the neurologist because of all the new drugs that are becoming available. The first edited recommendation stipulates that the entire spectrum of DMTs should be prescribed in appropriate centers with adequate infrastructures. To promptly detect side effects (consensus statements), patients should be monitored closely [76]. Since patients receive IM or IS over a long period of time, safety issues, including monitoring for malignancies, must be addressed.

Despite the fact that some drug treatments do not involve an extensive check-up, it seems wise to recommend that MS patients have systematic dermatological and gynecological follow-up, as in the case of a chest x-ray for tobacco users, or a fecal blood test for people over 50 years of age.

Most DMTs are officially contraindicated if the MS patient has a history of cancer (with the exception of basocellular carcinoma). Nevertheless, IFN-β and glatiramer acetate are allowed in this subtype of MS patients, but with reinforced follow-up. Generally, when a patient with MS is diagnosed with cancer, it is mandatory to discuss continuing DMT with the malignancy and to stop its use. If the cancer treatment includes chemotherapy, the cytotoxic drugs

Starting: Recommendation 7

Rationale

People presenting with a first demyelinating event who do not meet the 2010 International Criteria for MS are commonly encountered in clinical practice. Multiple prospective observational trials have consistently confirmed that people with a single clinical demyelinating event with two or more brain or spinal cord lesions remain at increased risk of a future MS diagnosis, with the highest risk incurred within five years of the initial event.[14–17] Evidence from multiple Class I and II trials confirms that DMTs are associated with a significant delay in second clinical relapse or new brain MRI-detected lesions in people with a first demyelinating event who are considered to be at high risk for MS on the basis of brain MRI-detected lesions. There is insufficient evidence concerning the comparative efficacy of specific DMTs for this purpose. Decisions concerning the selection of specific DMTs for people presenting with a first demyelinating event should abide by prescribing principles espoused in other recommendations. Individuals presenting with an incident demyelinating event who have no brain lesions are at low risk of a future MS diagnosis.

Level B	Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with two or more brain lesions that have imaging characteristics consistent with MS.
	After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and two or more brain lesions characteristic of MS who decide they want this therapy.

Fig. 1 Recommendation 7 about switching DMT and concerns about safety including cancers [79]. This recommendation is extracted from the American Academy of Neurology recommendations about disease modifying treatment in multiple sclerosis 2018. *DMT* disease-modifying therapies, *MS* multiple sclerosis, *PML* progressive multifocal leukoencephalopathy

used are, by class effect, active on MS; however, no studies confirm this. One of the trickiest questions for the next few years will be the integration of checkpoint inhibitors in the treatment of cancers, since they have been reported as being responsible for some fulminant forms of brain demyelination.

6 Conclusions

A review of the literature indicated the need for careful screening of MS patients requiring therapy. No risk of cancer has been reported with immunomodulators. For immunosuppressors, adherence to risk management plans outlined by regulatory agencies is mandatory, with the aim being to either deplete the total lymphocyte population or to selectively act on an activated target of MS. Close follow-up is required not only for all DMTs, such as fingolimod, natalizumab, or alemtuzumab, but also the newest IS, such as dimethyl fumarate, teriflunomide, daclizumab and ocrelizumab, and future upcoming IS drugs. Since the benefits are balanced by potential harmful effects, stringent follow-up of patients treated with IS as a target-to-treat strategy is recommended. DMTs could trigger cancer, therefore MS patients should have regular check-ups, focusing on monitoring the skin and breasts. MS patients have regular urinary tests and blood tests (hematological, thyroid) and brain MRIs as mandatory follow-up measures for some drugs. Consensual recommendations made by experts should be adopted, avoiding switching treatments for convenience. This has been clearly reinforced in the 2018 guidelines for DMT by the American Academy of Neurology (Fig. 1) [80]. Factors including long-term DMT use and family history should be considered during clinical monitoring of MS patients, including discussion about the risks of cancer. A strict long-term follow-up must be planned to avoid life-threatening conditions, including a long-term safety registry for all patients who participate in clinical trials for drug development.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this review.

Conflicts of interest Christine Lebrun has received honoraria for expertise and speaking from Biogen, Merck, Roche, Novartis, and Genzyme. Fanny Rocher has no conflicts of interest that are directly relevant to the content of this study.

References

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med. 2018;378(2):169–80.
2. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
3. Midgard R, Glattre E, Gronning M, Riise T, Edland A, Nyland H. Multiple sclerosis and cancer in Norway. A retrospective cohort study. Acta Neurol Scand. 1996;93:411–5.
4. Moller H, Kneller RW, BoiceJr JD, Olsen JH. Cancer incidence following hospitalization for multiple sclerosis in Denmark. Acta Neurol Scand. 1991;84:214–20.
5. Edan G, Le Page E. Induction therapy for patients with multiple sclerosis: Why? When? How? CNS Drugs. 2013;27(6):403–9.
6. Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Sorensen P, et al. A systematic review of the incidence and prevalence of cancer in multiple sclerosis. Mult Scler. 2015;21(3):294–304.
7. Handel AE, Ramagopalan SV. Multiple sclerosis and risk of cancer: a meta-analysis. J Neurol Neurosurg Psychiatry. 2010;81:1413–1414.
8. Gaindh D, Kavak KS, Teter B, Vuaghn CB, Cookfair D, Hahn T, et al. Decreased risk of cancer in multiple sclerosis patients and analysis of the effect of disease modifying therapies on cancer risk. J Neurol Sci. 2016;370:13–7.

9. Moisset X, Perié M, Pereira B, Dumont E, Lebrun-Frenay C, Lesage FX, et al. Decreased prevalence of cancer in patients with multiple sclerosis: a case-control study. PLoS One. 2017;12(11):e0188120.
10. Nielsen NM, Rostgaard K, Rasmussen S, Koch-Henriksen N, Storm HH, Melbye M, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. Int J Cancer. 2006;118(4):979–84.
11. Kyritsis AP, Boussios S, Pavlidis N. Cancer specific risk in multiple sclerosis patients. Crit Rev Oncol/Hematol. 2016;98:29–34.
12. Kingwell E, Bajdik C, Phillips N, Zhu F, Oger j, Hashimoto S, et al. Cancer risk in multiple sclerosis: findings from British Columbia, Canada. Brain. 2012;135(10):2973–2979.
13. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest. 2007;117(5):1137–46.
14. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol. 2011;29:235–71.
15. Bahmanyar S, Montgomery SM, Hillert J, Ekbom A, Olsson T. Cancer risk among patients with multiple sclerosis and their parents. Neurology. 2009;72(13):1170–7.
16. Fois AF, Wotton CJ, Yeates D, Turner MR, Goldacre MJ. Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's disease: record linkage studies. J Neurol Neurosurg Psychiatry. 2010;81(2):215–21.
17. Ragonese P, Aridon P, Vazzoler G, Mazzola MA, Lo Re V, Lo Re M, et al. Association between multiple sclerosis, cancer risk, and immunosuppressant treatment: a cohort study. BMC Neurol. 2017;17(1):155.
18. Sadovnick AD, Ebers GC, Dyment DA, Risch NJ. Evidence for genetic basis of multiple sclerosis. The Canadian collaborative study group. Lancet. 1996;347:1728–30.
19. Alonso A, Hernan MA, Ascherio A. Allergy, family history of autoimmune diseases, and the risk of multiple sclerosis. Acta Neurol Scand. 2008;117:15–20.
20. Holzmann C, Bauer I, Meyer P. Co-occurrence of multiple sclerosis and cancer in a BRCA1 positive family. Eur J Med Genet. 2013;56:577–9.
21. Lebrun C, Debouverie M, Vermersch P, Clavelou P, Rumbach L, de Seze J, et al. Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. Mult Scler. 2008;14(3):399–405.
22. Confavreux C, Saddier P, Grimaud J, Moreau T, Adeleine P, Aimard G. Risk of cancer from azathioprine therapy in multiple sclerosis: a case-control study. Neurology. 1996;46(6):1607–12.
23. Kingwell E, Evans C, Zhu F, Oger J, Hashimoto S, Tremlett H. Assessment of cancer risk with β-interferon treatment for multiple sclerosis. J Neurol Neurosurg Psychiatry. 2014;85(10):1096–102.
24. Lebrun C, Vermersch P, Brassat D, Defer G, Rumbach L, Clavelou P, et al. Cancer and multiple sclerosis in the era of disease-modifying treatments. J Neurol. 2011;258(7):1304–11.
25. Achiron A, Barak Y, Gail M, Mandel M, Pee D, Ayyagari R, et al. Cancer incidence in multiple sclerosis and effects of immunomodulatory treatments. Breast Cancer Res Treat. 2005;89:265–70.
26. Bloomgren G, Sperling B, Cushing K, Wenten M. Assessment of malignancy risk in patients with multiple sclerosis treated with intramuscular interferon beta-1a: retrospective evaluation using a health insurance claims database and postmarketing surveillance data. Ther Clin Risk Manag. 2012;8:313–21.
27. Sandberg-Wollheim M, Kornmann G, Bischof D, Moraga M, Hennessy B, Alteri E. The risk of malignancy is not increased in patients with multiple sclerosis treated with subcutaneous interferon beta-1a: analysis of data from clinical trial and postmarketing surveillance settings. Mult Scler. 2011;17:431–40.
28. Walker J, Smylie A, Smylie M. An association between glatiramer acetate and malignant melanoma. J Immunother. 2016;39(7):276–8.
29. Ghebeh H, Barhoush E, Tulbah A, Elkum N, Al-Tweigeri T, Dermine S. FOXP3+ Tregs and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: implication for immunotherapy. BMC Cancer. 2008;8:57.
30. Madray MM, Greene JF, Butler DF. Glatiramer acetate-associated, CD30+, primary, cutaneous, anapestic large-cell lymphoma. Arch Neurol. 2008;65(10):1378–9.
31. Buttmann M, Seuffert L, Mäder U, Toyka KV. Malignancies after mitoxantrone for multiple sclerosis: a retrospective cohort study. Neurology. 2016;86(23):2203–7.
32. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. Arthritis Rheum. 2010;62(1):9–21.
33. Mariette X, Cazals-Hatem D, Warszawki J, Liotte F, Balandraud N, Sibilia J, Investigators of the Club Rhumatismes et Inflammation. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. Blood. 2002;99(11):3909–15.
34. Xie X, Zhao Y, Ma C-Y, et al. Dimethyl fumarate induces necroptosis in colon cancer cells through glutathione depletion/ROS increase/MAPKs activation pathway. Br J Pharmacol. 2015;172:3929–43.
35. White C, Alshaker H, Cooper C, Winkler M, Pchejetski D. The emerging role of FTY720 (Fingolimod) in cancer treatment. Oncotarget. 2016;7(17):23106–27.
36. Huang O, Zhang W, Zhi Q, Xue X, Liu H, Shen D, et al. Teriflunomide, an immunomodulatory drug, exerts anticancer activity in triple negative breast cancer cells. Exp Biol Med. 2015;240(4):426–37.
37. Khan O, La Thangue NB. HDAC inhibitors in cancer biology: emerging mechanisms and clinical applications. 2011;90(1):85–94.
38. Hasanali ZS, Saroya BS, Stuart A, Shimko S, Evans J, Shah MV, et al. Epigenetic therapy overcomes treatment resistance in T cell prolymphocytic leukemia. Sci Transl Med,2015;7(293):293ra102.
39. Martinelli V, Cocco E, Capra R, et al. Acute myeloid leukemia in Italian patients with multiple sclerosis treated with mitoxantrone. Neurology. 2011;77(21):1887–95.
40. Ellis R, Boggild M. Therapy-related acute leukaemia with Mitoxantrone: what is the risk and can we minimise it? Mult Scler. 2009;15:505–8.
41. Marriott JJ, Miyasaki J, Gronseth G, O'Connor PW. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010;74:1463–70.
42. Le Page E, Leray E, Taurin G, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5-year follow-up observational study of 100 patients. J Neurol Neurosurg Psychiatry. 2008;79:52–6.
43. Hasan SK, Buttari F, Ottone T, et al. Risk of acute promyelocytic leukemia in multiple sclerosis: coding variants of DNA repair genes. Neurology. 2011;76:1059–65.
44. Reich K, et al. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. Arch Derm Research. 2015;307(10):875–83.
45. Landais A, Alhendi R, Gouverneur A, Teron-Aboud B. A case of lymphoma in a patient on teriflunomide treatment for relapsing multiple sclerosis. Mult Scler Relat Disord. 2017;17:92–4.

46. Herzinger T, Kleuser B, Schafer-Korting M, Korting HC. Sphingosine-1-phosphate signaling and the skin. Am J Clin Dermatol. 2007;8(6):329–36.
47. Kappos L, Radue LW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401.
48. Mahajan KR, Ko JS, Tetzlaff MT, Hudgens CW, Billings SD, Cohen JA. Merkel cell carcinoma with fingolimod treatment for multiple sclerosis: a case report. Mult Scler Rel Disord. 2017;17:12–4.
49. Killestein J, Leurs CE, Hoogervorst ELJ, van Eijk J, Mostert JP, van den Eertwegh AJM, et al. Five cases of malignant melanoma during fingolimod treatment in Dutch patients with MS. Neurology. 2017;89(9):970–2.
50. Cohen JA, Khatri B, Barkhof F, et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. J Neurol Neurosurg Psychiatry. 2016;87:468–75.
51. Papathemeli D, Gräfe R, Hildebrandt U, Zettl UK, Ulrich J. Development of a primary cutaneous CD30(+) anaplastic large-cell T-cell lymphoma during treatment of multiple sclerosis with fingolimod. Mult Scler. 2016;22:1888–90.
52. Cohan S, Godwin J, Gaedeke L. Acute lymphoblastic leukemia in a man treated with fingolimod for relapsing multiple sclerosis. J Investig Med High Impact Case Rep. 2015;3(1):2324709615575551.
53. Samaraweera AP, Cohen SN, Akay EM, Evangelou N. Lymphomatoid papulosis: a cutaneous lymphoproliferative disorder in a patient on fingolimod for multiple sclerosis. Mult Scler. 2016;22:122–4.
54. Walker S, Brew B. Kaposi sarcoma in a fingolimod-treated patient with multiple sclerosis. J Clin Neurosci. 2016;31:217–8.
55. Lebrun-Frenay C, Papeix C, Kobelt G, Visy JM, Coustans M, Debouverie M, et al. Long-term efficacy, safety, tolerability and quality of life with fingolimod treatment in patients with multiple sclerosis in real-world settings in France: VIRGILE two-year results. 2017. ECTRIMS 2017; Paris, EP1716.
56. Hassan R, Gupta M, Kern W, Ozer H. Acute myeloid leukemia following treatment with cladribine for hairy cell leukemia: a case report and review of the literature. Leuk Lymphoma. 2004;45(10):2149–52.
57. Robak T, Blonski JZ, Gora-Tybor J, Kasznicki M, Konopka L, Ceglarek B, et al. Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. Eur J Cancer. 2004;40(3):383–9.
58. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sorensen PS, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362:416–26.
59. Pakpoor J, Disanto G, Altmann DR, Pavitt S, Turner BP, Marta M, et al. No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. Neurol Neuroimmunol Neuroinflammation. 2015;2(6):e158.
60. Rosenberg JD, Burian C, Waalen J, Saven A. Clinical characteristics and long-term outcome of young hairy cell leukemia patients treated with cladribine: a single-institution series. Blood. 2014;123:177–83.
61. Coles AJ, Cohen JA, Fox EJ, Giovannoni G, Hartung HP, Havrdova E, et al. Alemtuzumab CARE-MS II 5-year follow-up. Neurology. 2017;89(11):1117–26.
62. Havrdova E, Arnold DL, Cohen JA, Hartung HP, Fox EJ, Giovannoni G, et al. Alemtuzumab CARE-MS I 5-year follow-up. Neurology. 2017;89(11):1107–16.
63. Pace AA, Zajicek JP. Melanoma following treatment with alemtuzumab for multiple sclerosis. Eur J Neurol. 2009;16(4):e70–1.
64. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899–910.
65. Bergamaschi R, Montomoli C. Melanoma in multiple sclerosis treated with natalizumab: causal association or coincidence? Mult Scler. 2009;15(12):1532–3.
66. Castela E, Lebrun-Frenay C, Laffon M, Rocher F, Cohen M, Leccia NC, Bahadoran P, Lacour JP, Ortonne JP, Passeron T. Evolution of nevi during treatment with natalizumab: a prospective follow-up of patients treated with natalizumab for multiple sclerosis. Arch Dermatol. 2011;147(1):72–6. https://doi.org/10.1001/archdermatol.2010.243.
67. Sartori D, Grundmark B. Natalizumab and rapidly evolving central nervous system lymphoma. In: WHO pharmaceuticals newsletter, no. 6. World Health Organization; 2017. p. 14.
68. Wynn D, Kaufman M, Montalban X, Vollmer T, Simon J, Elkins J, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9(4):381–90.
69. Kappos L, Wiendl H, Selmaj K, Boyko A, Kaufman M, Rose J, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2015;373(15):1418–28.
70. Gold R, Radue EW, Giovannoni G, Selmaj K, Hardrova E, Stefoski D, et al. Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study. BMC Neurol. 2016;16:117.
71. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med. 2017;376(3):209–20.
72. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221–34.
73. van Vollenhoven RF, Emery P, Bingham CO, Keystone EC, Fleischmann RM, First DE, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. 2013;72(9):1496–502.
74. Yudkin PL, Ellison GW, Ghezzi A, Goodkin DE, Hughes RA, McPherson K, et al. Overview of azathioprine treatment in multiple sclerosis. Lancet. 1991;338(8774):1051–5.
75. Casetta I, Iuliano G, Filippini G. Azathioprine for multiple sclerosis. Cochrane database Syst Rev. 2007;4:CD003982.
76. Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger TA Jr. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control follow-up study. Am J Med. 1987;83(1):1–9.
77. De Ridder D, et al. Bladder cancer in patients with multiple sclerosis treated with cyclophosphamide. J Urol. 1998;159(6):1881–4.
78. Le Bouc R, Zéphir H, Majed B, Verier A, Marcel M, Vermersch P. No increase in cancer incidence detected after cyclophosphamide in a French cohort of patients with progressive multiple sclerosis. Mult Scler. 2012;18(1):55–63.
79. Montalbán X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. 2018;24(2):96–120. https://doi.org/10.1177/1352458517751049.
80. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS, et al. Practice guideline recommendations summary: disease modifying therapies for adults with multiple sclerosis. Neurology. 2018;90:777–88.